UNIT-II

Regulatory Approval Process

Points to be covered in this topic

- ❑ Approval processes and timelines involved in Investigational New Drug (IND)
- ❑ New Drug Application (NDA)
- ❑ Abbreviated New Drug Application (ANDA)
- ❑ Changes to an approved NDA/ANDA

Approval processes and timelines involved in Investigational New Drug (IND)

❑ INTRODUCTION

- An **experimental novel drug** is a new **pharmacological or biological** agent that is employed in a clinical trial.
- This term also encompasses biological products utilised in vitro for **diagnostic purposes.**
- The **Investigational New Drug Application (IND)** is a request for an exemption from the federal statute that **bans an unapproved drug** from **being delivered in interstate commerce.**

❑ TYPES OF INDs :

- **Commercial INDs**
- **Non-commercial INDs**

❖ **Commercial INDs :** These are applications submitted mostly by firms in order to acquire marketing permission for a new product.

❖ **Non-Commercial INDs :** These INDs are for non-commercial research purposes only. These are :

- **Investigator's INDs :** An investigator IND is submitted by a physician who begins and conducts an investigation and is directly responsible for the administration or dispensing of the investigational medicine.

- **Emergency Use INDs :** In Case of Emergency the IND permits the FDA to authorise the use of an experimental drug in an emergency scenario if there is insufficient time to submit an IND. It is also used for patients who do not match the criteria of an established study protocol.
- **Treatment IND :** While the final clinical work is being completed and the FDA evaluation is taking place, a treatment IND is submitted for investigational medications that have shown promise in clinical testing for serious or immediately life-threatening disorders.

The IND application must include information in three major categories:

(i) Animal Pharmacology and Toxicology Studies : Preliminary data to determine whether the product is reasonably safe for human testing.

(ii) Manufacturing information : Information on the drug's composition, producer, stability, and controls used to verify that the company can effectively make and distribute consistent batches of the drug.

(iii) Clinical protocol and investigator information : Detailed protocols for proposed clinical research to ensure that volunteers are not exposed to unnecessary dangers. Additionally, information about the investigation's qualifications if they complete their clinical tasks.

➢ **In IND must also include The Investigator's brochure**

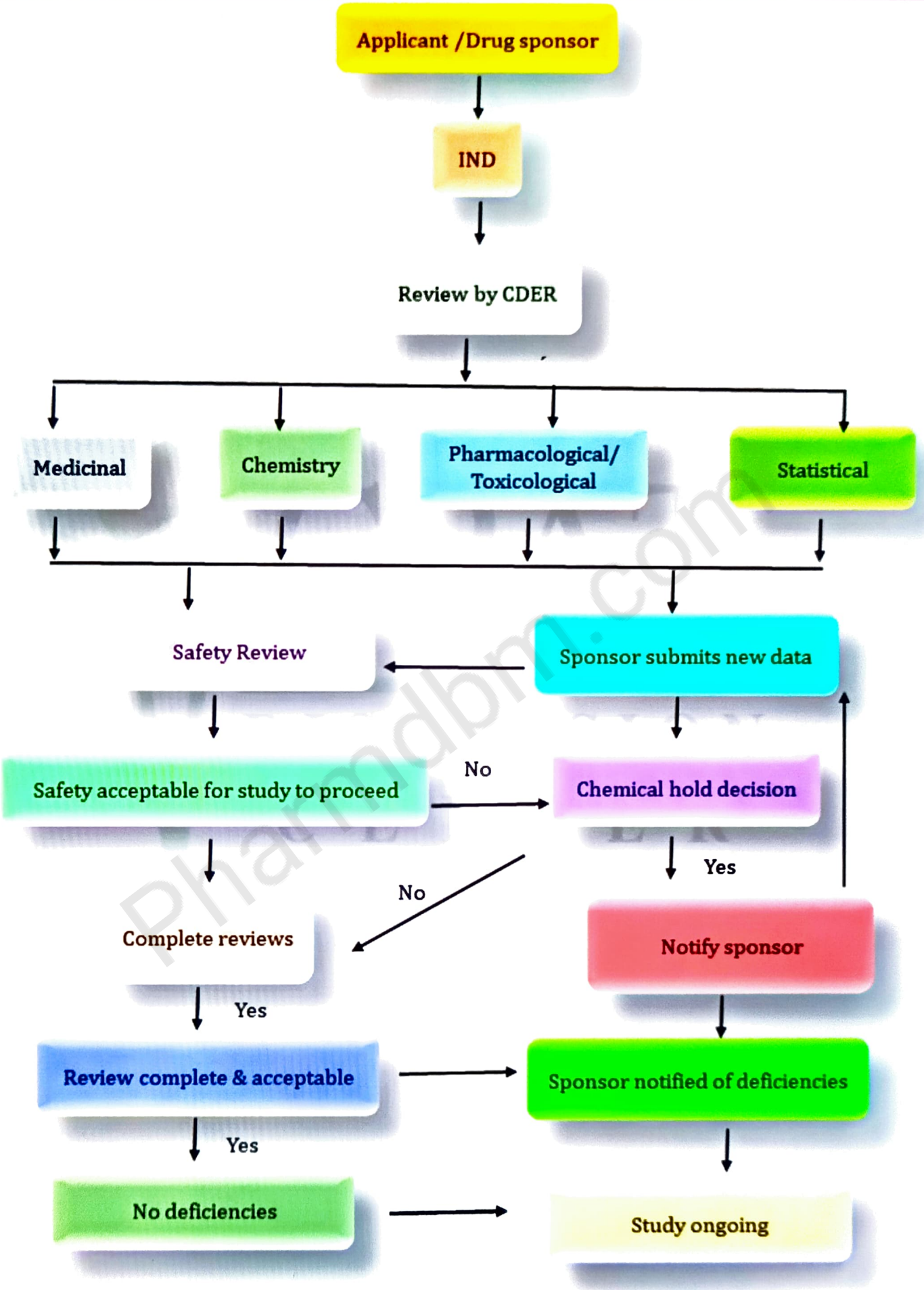


Fig. Investigational New Drug Application

New Drug Application (NDA)

❑ INTRODUCTION

- The **NDA application** is the **vehicle** by which **medication sponsors** formally request that the **FDA approve a novel medicine for sale and marketing in the United States.**
- A **new drug application (NDA)** is a detailed document that must be filed to the **Food and Drug Administration (FDA)** in order to obtain approval to market a new drug in the United States.

❖ The NDA's goals are to offer enough material for FDA reviewers to make the following essential conclusions :

- Whether the drug is safe and effective in its suggested usage, and whether the benefits exceed the dangers.
- Whether the proposed labelling (package insert) for the drug is reasonable, and what it should include.
- Whether the production procedures and quality controls employed to maintain the drug's identity, strength, quality, and purity are appropriate.

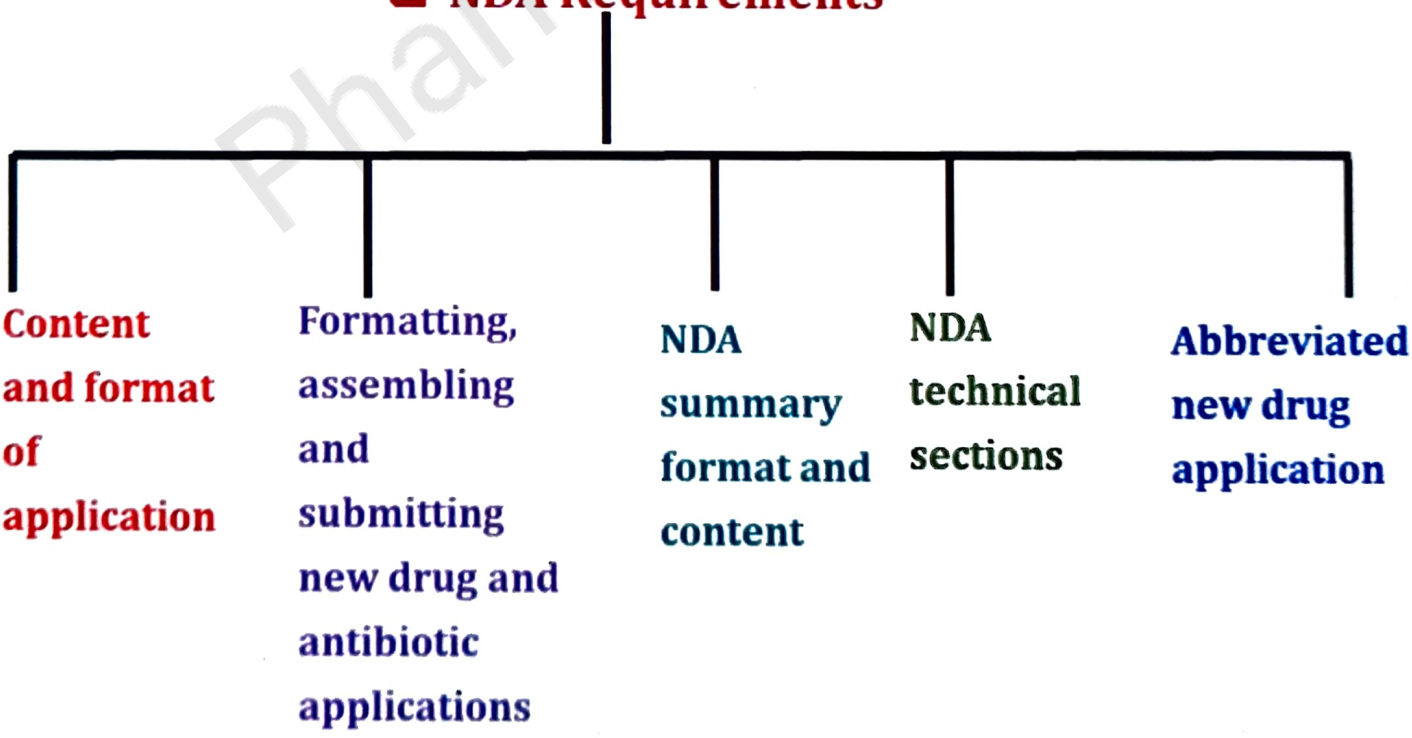
❖ The Centre for Drug Evaluation and Research (CDRE) categorises new drug applications based on the type of medicine being submitted and its intended usage

- New Molecular Entity
- New Salt of Previously Approved Drug
- New Formulation of Previously Approved Drug
- New Combination of Two or More Drugs
- Already Marketed Drug Product – Duplication by new manufacturer
- New Indication for Already Marketed Drug, including switch in status to OTC (conversion of prescription drug to OTC)
- Already Marketed Drug Product without previously Approved NDA

❖ **Depending on the type and nature of the drug, the following four types of applications are submitted in the United States for drug marketing authorisation**

1. **New Drug Application (NDA)**
2. **Biological License Application**
3. **Application u/s 505(b) (2)- paper NDA**
4. **Supplement New Drug Application (SNDA)**

❑ **NDA Requirements**



1. Content and format of application : Although the exact standards vary depending on the nature of the drug, the NDA must include all essential data and information gathered by the sponsor during the product's research and development.

2. Formatting, assembling and submitting new drug and antibiotic applications :

A. Application format : Archival and Review copies are required per NDA standards.

(i) Archival copy : This is a comprehensive copy of an application submission designed to serve as a reference source for FDA reviewers. This includes information that was not included in the review copy.

(ii) Review copy : It is organised into five (or six) sections that comprise the technical and scientific information requested by FDA reviewers. Each review copy part is bound separately. It must include the following: A copy of your cover letter. A copy of the application form(FDA 356h). A copy of the overall overview a copy of the application's index an index to the specific review section Both copies are submitted on paper.

B. Assembling the application :

3. NDA Summary Format and Content : A summary should be detailed enough. Data should be provided in the form of a **table or a graph**. **The length of the summary should be between 50 and 200 pages.**

(i) Annotated package insert : This section contains the **proposed text** for the **product's labelling**. The proposed package labelling language must include a reference to volume and page number to the material in the summary and technical parts of the applications.

(ii) Pharmacological class, scientific rationale, intended use and potential clinical benefits : A concise statement should be included to **identify the drug's pharmacological class**, **scientific basis**, **intended usage**, and **potential clinical advantages**.

(iii) Chemistry, Manufacturing and Controls

→ **Drug substance :** It provides a description of the drug substance, its physical and chemical properties, and its stability

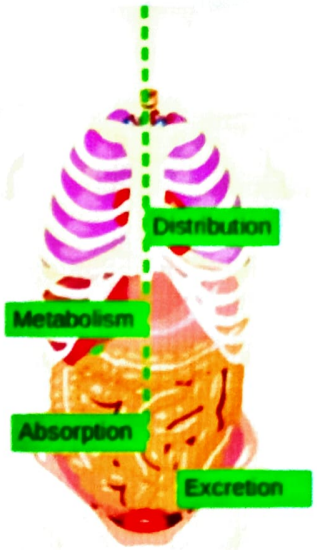
→ **Drug product :** It includes information about :

- ✓ Composition and dosage form
- ✓ Name and address of manufacturer
- ✓ Container and closure system
- ✓ Stability
- ✓ Specifications for drug product and test methods to assure the specifications

(iv) Foreign Marketing History : The marketing history should be supplied if the product is marketed outside the United States, regardless of the dosage form, strength, salt, ester, or complex of the medicine.

(v) Non- clinical Pharmacology and Toxicology Summary : It contains information about

- ✓ **Pharmacology studies**
- ✓ **Acute toxicity studies**
- ✓ **Multi dose toxicity studies**
- ✓ **Carcinogenicity studies**
- ✓ **Special toxicity studies**
- ✓ **Reproduction studies**
- ✓ **Mutagenicity studies**
- ✓ **ADME studies**



(vi) Human Pharmacokinetics and bio-availability Summary : It comprises a brief explanation of the **drug's bioavailability study, pharmacokinetic characteristics of the active ingredient,** and dissolving profile.

(vii) Microbiology Summary : It summarises the findings of **microbiologic experiments with anti-infective and antiviral drugs.** This comprises the drug's mechanism of action, antimicrobial spectrum of action, and mechanism of resistance.

(viii) Clinical Data Summary and Results of Statistical Analysis : An NDA will be approved based on efficacy and safety. The Clinical Data Summary and Statistical Analysis Results are separated into numerous sections, as indicated below:

- ✓ **Clinical pharmacology**
- ✓ **Overview of Clinical Studies**
- ✓ **Controlled Clinical Studies**
- ✓ **Uncontrolled Clinical Studies**
- ✓ **Information Safety summary**

4. NDA technical sections : This includes brief description of the following sections.

(i) Chemistry, Manufacturing and Controls : It is the most important section of an NDA or ANDA. This section must completely detail the drug substance (active ingredient), its synthesis (or isolation), and purification, as well as any applicable process controls, specifications, and analytical test procedures.

(i) Nonclinical Pharmacology and Toxicology : It describes or summarises all animal and in vitro investigations with the medication.

- ✓ Pharmacology Studies
- ✓ Acute Toxicity Studies
- ✓ Sub chronic/Chronic/Carcinogenicity Studies Special Toxicity Studies Reproduction Studies
- ✓ Mutagenicity Studies
- ✓ ADME Studies

(iii) Human Pharmacokinetics and bio-availability Section : It is preferable for a new chemical entity (NCE) to ascertain its bioavailability and pharmacokinetics from the dosage form, except for some dosage forms (e.g., intravenous solutions), where 100% bioavailability can be assumed.

(iv) Microbiology : This part is critical for anti-infective medications since it contains information on the molecular foundation of the drug's action and its antimicrobial spectrum, as well as any known causes of drug resistance and clinical laboratory tests.

(v) Clinical Data Section : It is the most essential and intricate section of an NDA.

- **It includes**
- List of investigators; List of INDs and NDAs
- Background / Overview of clinical investigations
- Clinical pharmacology
- Controlled clinical studies
- Uncontrolled clinical studies
- Other studies and information
- Integrated summary of efficacy
- Integrated summary of safety
- Drug abuse and over dosage information
- Integrated summary of benefits and risk of drugs

(vi) Samples, Methods Validation and Labeling : Samples should not be submitted to the FDA together with the application. The reviewing chemist will contact the applicant and offer the laboratory address where samples should be sent.

(vii) Case Report Forms and Tabulations : The sponsor must submit data tabulations from each Phase II and Phase III study, as well as the case study report form, for each clinical trial patient who died or dropped out due to an adverse event.

(viii) Patent Information : Any patent held by the sponsor that covers the drug material, formulation, and composition of the drug product, or method of use, must be submitted.

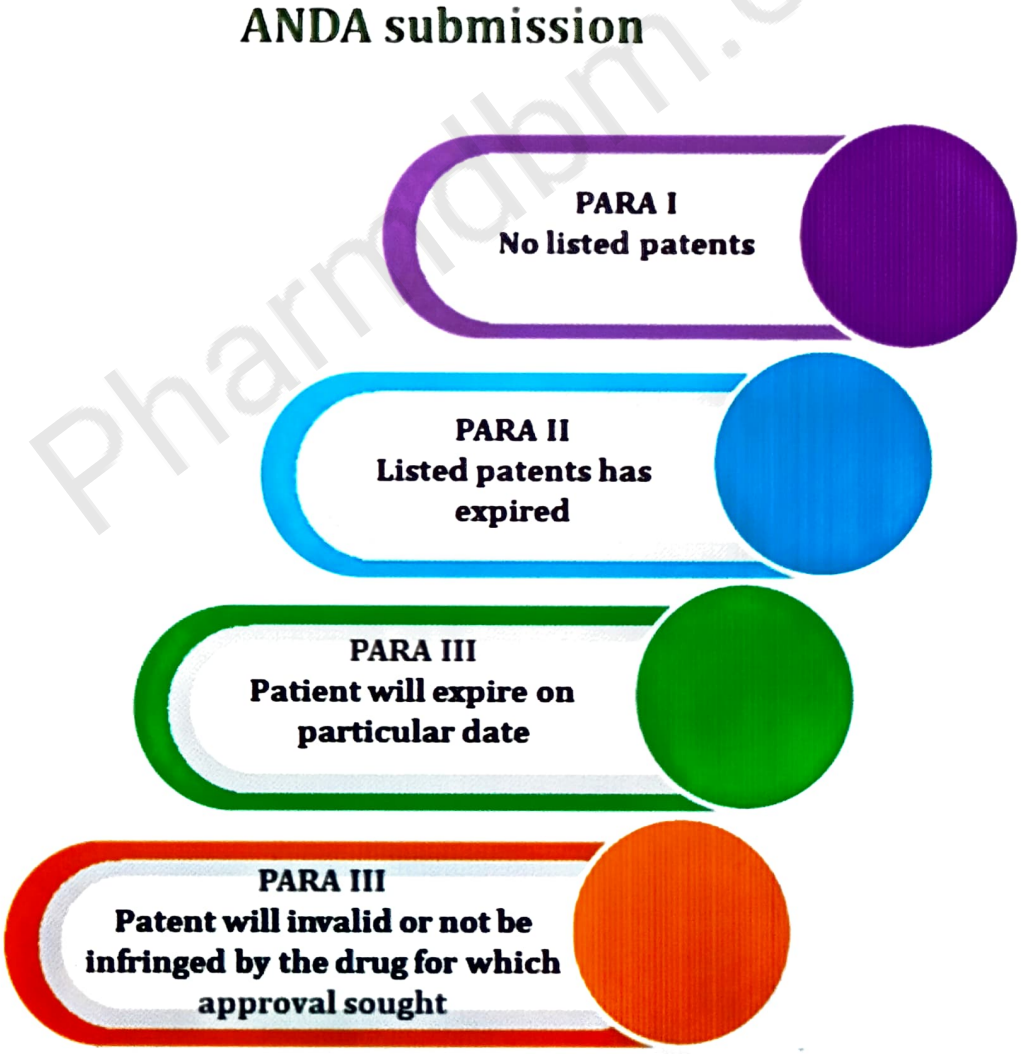
5. Abbreviated new drug application : An abbreviated new drug application (ANDA) contains data that is submitted to the FDA for assessment and eventual approval of a generic medicine product. Once approved, an application may produce and market the generic drug product to provide a safe, effective, and lower-cost alternative. It refers to the brand-name medication.

Abbreviated new drug application (ANDA)

❑ INTRODUCTION

❖ **Abbreviated new drug application :** An abbreviated new drug application (ANDA) contains data that is **submitted to the FDA** for assessment and eventual approval of a generic medicine product. Once approved, an application may produce and market the generic drug product to provide a safe, effective, and lower-cost alternative. It refers to the brand-name medication.

❖ Types of ANDA



❑ Code of Federal Regulation

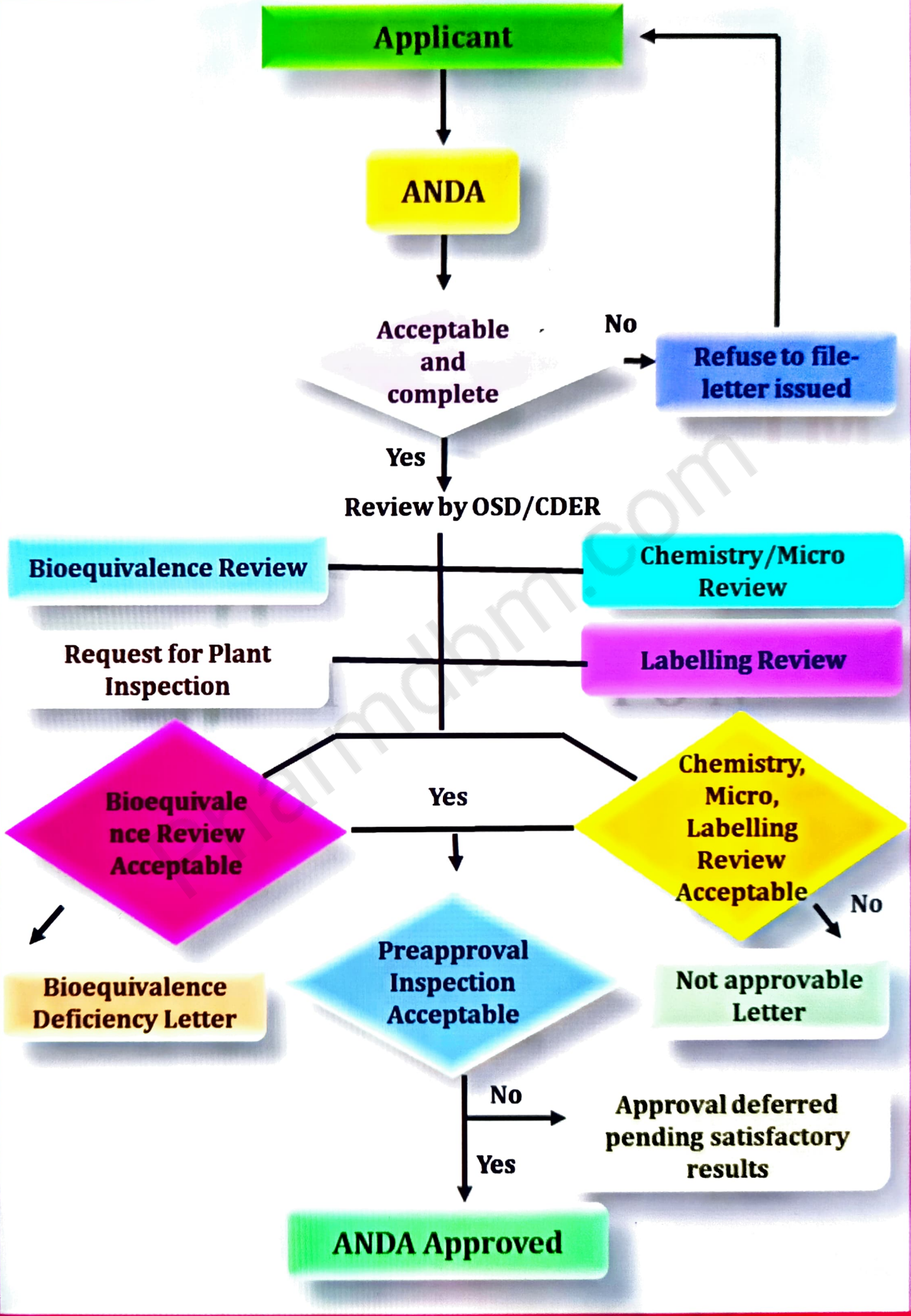
The following regulations apply to ANDA process:

- **21 CFR 314** - Application to FDA approval to market a New Drug or Antibiotic Drug
- **21 CFR 320** - Bioavailability and Bioequivalence requirements
- **21 CFR 310** – New Drugs
- **Office of Generic Drug (OGD)** strongly encourages submission of bioequivalence, chemistry and labelling portions of the application in electronic format.

❑ Format and content of ANDA

The abbreviated application must be submitted in three copies: an archival copy, a review copy, and a field copy. An archival copy must include the following:

- Application form
- Table of contents
- Basis for ANDA submission
- Condition of use
- Active ingredients
- Route of administration
- Dosage form and strength
- Bioequivalence and bioavailability
- Labelling
- Chemistry, manufacturing and controls
- Samples
- Patent certification
- Financial certification or disclosure statement
- Other information


Applicant
ANDA
Acceptable and complete
No
Refuse to file- letter issued
Yes
Review by OSD/CDER
Bioequivalence Review
Chemistry/Micro Review
Request for Plant Inspection
Labelling Review
Bioequivalence Review Acceptable
Yes
Chemistry, Micro, Labelling Review Acceptable
No
Bioequivalence Deficiency Letter
Preapproval Inspection Acceptable
Not approvable Letter
No
Approval deferred pending satisfactory results
Yes
ANDA Approved

❑ Difference between Submission of NDA and ANDA

NDA requires submission of:

(i) Well-controlled clinical studies to demonstrate effectiveness
(ii) Preclinical and clinical data to show safety
(iii) Details of manufacturing and packaging
(iv) Proposed annotated labelling

In contrast, ANDA requires submission of:

(i) Detailed description of components
(ii) Manufacturing, controls, packaging, data to assure bioequivalence and bioavailability and labelling. Labelling should be prepared in accordance with DESI (Drug Efficacy Study Implementation)

Exclusivity:

Exclusivity is a statutory provision designed to promote a balance between an Innovator and Generic drug competitor. As long as a drug patent lasts, a reference listed drug company enjoys a period of market exclusively or monopoly. Expiration of patent removes the monopoly of the patent holder.

Terms of Exclusivity:

Orphan drug - 7 years
New chemical entity – 5 years
Pediatric exclusivity – 6 months additional
Patent challenge – 180 days

Changes to an approved NDA/ANDA

This guideline gives recommendations to holders of NDAs and ANDAs who plan to make post-approval revisions in conformity with section 506A of the Federal Food, Drug, and Cosmetic Act and 314.70 (21 CFR 314.70). It supersedes the previous guidance provided under the same title in November 1999.

✓ Recommendations are provided for post approval changes in:

- Components and composition
- Manufacturing sites
- Manufacturing process
- Specifications
- Container closure system
- Labeling
- Miscellaneous changes
- Multiple related changes

❑ Reporting categories

A **major change** is one that has a significant potential to have an undesirable influence on the identity, strength, quality, purity, or potency of a drug product, as these factors may relate to the safety or effectiveness of the drug product.

Prior Approval Supplement: An applicant may request that FDA accelerate its consideration of a prior approval supplement for public health reasons (e.g., drug shortage).

A **Moderate change** that has a modest risk of affecting the identity, strength, quality, purity, or potency of the drug product, as these factors may be related to the medicine's safety or effectiveness.

✓ **There are two types of moderate changes, which include**

Change requiring the submission of a supplement – changes being effected in 30 days

Change requiring the submission of supplement – change being effected

A **minor change** is change that has **minimal potential** to have an **adverse effect** on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

➢ Changes in components

Changes in components and composition that may require a **changes-being-effected supplement** or an annual report are not addressed in this guidance document. The Agency states that these recommendations are far too complex, but may be covered in one or more guidance documents regarding post approval changes (e.g. SUPAC documents)

➢ Manufacturing Sites

If a drug maker **changes to a manufacturing** site other than those specified in the approved application CDER must be notified. These sites can include those used by an applicant to:

- Manufacture or process drug products in process materials, drug substances or drug substance intermediates
- Package drug products
- Label drug products
- Test components drug product containers, closures packaging materials, in-process materials or drug products

➢ Manufacturing process

According to the guidance document, "The **potential for adverse effects on the identity, strength, quality, purity, or potency** of a drug product as these factors may relate to the safety or effectiveness of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product.

➢ Specification

In its guidance, FDA defines specifications as: "The **quality standards provided in an approved application to confirm the quality of drug substances,** drug products. intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product."

➢ Container Closure System

The potential that **a change in a product's container closure system will have an adverse effect** on the identity, strength, quality, purity, or potency of the drug's safety or effectiveness is generally dependent on the following:

- Drug's route of administration.
- Performance of the container closure system.
- Likelihood of interaction between the packaging component and the dosage form.

➢ Labelling

A challenge in drugs labelling includes changes in one of the following :

- Package inserts
- Package labelling
- Container label

➢ Multiple Related Changes

Involves various combination of individual changes. If an applicant has multiple related changes that fall into different recommended reporting categories, "CDER recommends that the submission be in accordance with the reporting category for the individual changes."

Variation	Types	Anticipated Implementation	Guideline approval time
Minor	Annual Report (AR)	Up to 1 year before submission	N/A
Moderate	CBE – 0	On receipt of submission by FDA	N/A
	CBE – 30	30 days after receipt of submission	6 MONTHS
Major	Prior Approval Supplement (PAS)	Up to 6 months after submission	4 MONTHS